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CASE REPORT

Application of the model-informed drug development paradigm to datopotamab deruxtecan dose selection for late-stage development

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Abstract

To replace the conventional maximum tolerated dose (MTD) approach, a paradigm for dose optimization and dose selection that relies on model-informed drug development (MIDD) approaches has been proposed in oncology. Here, we report our application of an MIDD approach during phase I to inform dose selection for the late-stage development of datopotamab deruxtecan (Dato-DXd). Dato-DXd is a TROP2-directed antibody-drug conjugate being developed for advanced/metastatic non-small cell lung cancer (NSCLC) and other tumors. Data on pharmacokinetics (PKs), efficacy, and safety in NSCLC were collected in the TROPION-PanTumor01 phase I dose-expansion and -escalation study over a wide dose range of 0.27–10 mg/kg administered every 3 weeks. Population PK and exposure–response analyses were performed iteratively at three data cutoffs to inform dose selection. The 6 mg/kg dose was identified as the optimal dose by the second data cutoff analysis and confirmed by the subsequent third data cutoff analysis. The 6 mg/kg dose was more tolerable (i.e., lower rates of interstitial lung disease, stomatitis, and mucosal inflammation) than the MTD (8 mg/kg) and was more efficacious than 4 mg/kg (simulated mean objective response rate: 23.8% vs. 18.6%; mean hazard ratio of progression-free survival: 0.74) – a candidate dose studied just below 6 mg/kg. Therefore, the 6 mg/kg dose was judged to afford the optimal benefit–risk balance. This case study demonstrated the utility of an MIDD approach for dose optimization and dose selection.

INTRODUCTION

The existing paradigm in oncology drug development to find the maximum tolerated dose (MTD) is based on the notion that an increased dose leads to increased tumor suppression. This paradigm may not be applicable to targeted therapies or antibody-drug conjugates, which are directed against specific molecular targets.[1] For such therapies, the dose exposure–response (E–R) curves for efficacy and toxicity generally have distinct patterns; efficacy

saturates at a certain dose, but toxicity may continue to increase with dose escalation.[2] Thus, these therapies can often be administered at a dose that maximizes efficacy and limits toxicity. Aligned with US Food and Drug Administration Project Optimus,[3] an initiative for reforming the dose optimization and dose-selection paradigm in oncology,[2] the current efforts evaluated multiple dosages to determine an optimal dose for late-stage development of datopotamab deruxtecan (Dato-DXd; DS-1062a) in advanced or metastatic non-small cell lung cancer (NSCLC).

Dato-DXd is composed of a humanized anti-TROP2 IgG1 monoclonal antibody covalently linked to an exatecan derivative (deruxtecan; DXd) – a highly potent topoisomerase I inhibitor payload – via a stable, tumor-selective, tetrapeptide-based cleavable linker.[4] Dato-DXd has demonstrated encouraging antitumor activities and a manageable safety profile in heavily pretreated patients with NSCLC relapsed or refractory to standard therapy in the first-in-human, dose-escalation and -expansion study, TROPION-PanTumor01 (NCT03401385).[5] The dose-escalation part evaluated 0.27, 0.5, 1, 2, 4, 6, 8, and 10 mg/kg doses administered once every 3 weeks (q3w). The MTD was established as 8 mg/kg q3w.[6,7] Efficacy signals (tumor response) emerged at 2 mg/kg and appeared stronger at higher doses (4, 6, and 8 mg/kg).[8]

To characterize the E–R relationship and identify an optimal dose, several doses were evaluated, starting with 8 mg/kg, followed by 6 mg/kg and 4 mg/kg. The targeted number of patients with NSCLC were 50, 50, and 80 for 4, 6, and 8 mg/kg, respectively. Iterative population pharmacokinetic (PopPK) and E–R analysis of efficacy and safety were performed at multiple data cutoffs (DCOs) to inform and confirm selection of the optimal dose.

Key question

What dose would offer optimal benefit–risk balance in NSCLC and be viable for late-stage development?

Analysis plan

PopPK and E–R analyses were conducted for two interim DCOs (March 4, 2020, and January 8, 2021) and one final DCO (July 30, 2021) in the NSCLC cohorts in TROPION-PanTumor01. See Table S1 for the analysis components.

Data

This study was conducted in compliance with the protocol, ethical principles of the Declaration of Helsinki, International Council for Harmonization consolidated Guideline E6 for Good Clinical Practice (CPMP/ICH/135/95), and applicable regulatory requirements. All patients signed informed consent forms approved by independent ethics committees or institutional review boards at each site.

Plasma concentrations of Dato-DXd and DXd were measured per the sampling schedule (details in File S1) Tumor size was measured at screening, every 6 weeks up to week 36, and thereafter every 12 weeks while the patient remained on Dato-DXd. Tumor response was evaluated by blinded independent central review (BICR) using RECIST version 1.1, and objective response rate (ORR) and progression-free survival (PFS) were determined. Safety data for analysis included treatment-emergent adverse events (TEAEs; graded per the National Cancer Institute Common Toxicity Criteria for Adverse Events version 5.0).

PopPK analysis

PopPK model development followed a stepwise approach: the model for intact Dato-DXd was established first. Then, with all Dato-DXd–related parameters fixed, the model for DXd was developed. In each step, modeling progressed from the base model to the full covariate model and then to the final model. The structural models for Dato-DXd and DXd were determined based on their concentration profiles, prior knowledge,[9] and model performance (Figure S1). Preselected covariates for evaluation of Dato-DXd – based on pharmacological plausibility and clinical interest – included weight, age, plasma albumin level, estimated glomerular filtration rate, baseline tumor size, sex, race, Eastern Cooperative Oncology Group performance status (ECOG-PS), hepatic function, and antidrug antibody status (Table S2); the covariates for DXd are listed in Table S3. From the final PopPK model, individual post hoc exposure metrics were derived for E–R analyses (details in File S1).

E–R analysis of efficacy

Efficacy end points for analysis included BICR-assessed, confirmed ORR and PFS. The ORR was analyzed using logistic regression driven by the average concentration (C_{avg}) of Dato-DXd to response (or to the end of the last dosing cycle of nonresponders). The PFS analysis included (1) Kaplan–Meier plots stratified by Dato-DXd C_{avg} to event; (2) plots of time-varying exposure (cycle-wise area under the curve [AUC_{tau}] over time) in patients with PFS events (progression/death) overlaid on AUC_{tau} in all patients at risk[10]; and (3) time-varying Cox proportional hazards modeling driven by AUC_{tau}. Dose modifications,

including dose reduction and dose delay, were observed in TROPION-PanTumor01. Therefore, metrics that took dosing history into consideration (e.g., C_{avg} and cycle-wise AUC_{tau}) were considered more appropriate for the current E–R analysis than static exposure metrics (e.g., cycle 1 or steady-state AUC_{tau}). Covariates included in the ORR and PFS analysis were age, baseline tumor size, number of prior lines of therapy, last prior line of therapy being an immuno-oncology (IO) agent, smoking, actionable genetic alterations, ECOG-PS, history of brain metastases, sex, and country (Table S4 and File S1). E–R overall survival (OS) analysis using AUC_{tau} and Cox proportional hazards modeling demonstrated a lack of E–R relationship for OS. The OS results were immature at the time of dose selection and, as such, did not inform dose selection in this study.

E–R analysis of safety

Safety end points for analysis included stomatitis, ocular surface toxicity (e.g., dry eye, decreased or blurred vision, photophobia, keratitis, and corneal ulcer), adjudicated interstitial lung disease (ILD), TEAE-related dose modifications (dose reduction and dose interruption), drug withdrawal, grade greater than or equal to three TEAEs, serious TEAEs, mucosal inflammation, fatigue, alopecia, rash, gastrointestinal toxicity (nausea, vomiting, diarrhea, and appetite decreased), and hematological toxicity (anemia, leukopenia, neutropenia, thrombocytopenia, and lymphopenia). Logistic regression was conducted for all TEAEs, and time-to-event analysis using Cox proportional hazards modeling was performed for stomatitis, ocular surface toxicity, ILD, and mucosal inflammation. Initial explorations examined Dato-DXd and DXd exposure metrics, such as cycle 1 maximum and trough concentration, AUC, and C_{avg} to the end of event cycles in which the event occurred (to account for dose reductions or interruptions). For the final model, the best exposure metrics for each safety end point, based on the standard diagnostic criteria, were selected. A stepwise approach was used to evaluate the effects of these covariates: age, sex, ECOG-PS, country, number of prior lines of therapy, last prior line of therapy being IO, smoking, and baseline laboratory measures for the respective hematological end points (File S1).

Benefit–risk assessment simulations

Simulations using the final PopPK, efficacy, and safety models were conducted at the 2, 3, 4, 6, and 8 mg/kg Dato-DXd doses, q3w, to enable benefit–risk assessment and selection of optimal dose. Simulations at each dose were run in the pooled NSCLC population ($N = 210$) from TROPION-PanTumor01, balancing out the covariate effects across doses. The following parameters were generated from simulations: (1) exposure metrics of Dato-DXd and DXd; (2) probability of objective response; (3) hazard ratio (HR) for progression/death at different doses relative to the 4 mg/kg dose; (4) median PFS time; (5) probabilities of TEAEs; and (6) HR for experiencing stomatitis, ocular surface toxicity, ILD, or mucosal inflammation at different doses relative to the 4 mg/kg dose (more details in File S1).

RESULTS AND IMPACT ASSESSMENT

Overview of the efficacy and safety data from the first DCO was provided by Lisberg et al.[6] Tumor response data were mostly from 8 mg/kg Dato-DXd ($n = 60$), with fewer data available from the 4 mg/kg ($n = 6$) and 6 mg/kg ($n = 19$) doses. A positive E–R relationship for ORR was identified. ILD emerged as a new adverse event, especially at the 8 mg/kg dose. The safety profile at the 8 mg/kg dose became less acceptable due to ILD risk, although 76 of the planned 80 patients were already enrolled. Enrollment in the 8-mg/kg cohort during dose expansion was stopped once it became apparent that 8 mg/kg was the MTD, thus accounting for the relatively large 8-mg/kg sample size compared to 4- and 6-mg/kg cohorts.

Analysis of the second DCO enabled benefit–risk assessment across doses and informed the selection of 6 mg/kg Dato-DXd for further development. Meric-Bernstam et al.[5] observed ORR and median PFS to be comparable at the 4, 6, and 8 mg/kg doses, whereas TEAE-associated dose modifications and discontinuation, ILD, and stomatitis/mucosal inflammation were more prevalent and/or more severe at 8 mg/kg than at the lower doses, resulting in rejection of 8 mg/kg for further development. There were no specific safety thresholds predetermined for the observed adverse events, as the totality of evidence was used for decision-making. ILD was an important consideration when evaluating risk alongside other safety end points. Rates of ILD were higher with 8 mg/kg (15%), whereas they were similar with the 4 and 6 mg/kg doses (10% and 8%, respectively). E–R analysis results for ORR, PFS ($n = 209$), and stomatitis/mucosal inflammation were presented by Lu et al.[11] The E–R model–based simulations suggested a trend of higher ORR (23.4%, 90% confidence interval [CI]: 18.4%–29.1% vs. 18.7%, 90% CI: 14.4%–23.6%) and lower risk of progression/death (HR: 0.77; 95% CI: 0.70–0.84) at the 6 mg/kg dose relative to the 4 mg/kg dose.

These pharmacometric results and clinical observations suggested that 6 mg/kg demonstrated an optimal benefit–risk balance.

The in-depth analysis presented here of the final DCO provided consistent results for the PopPK and E–R analysis for Dato-DXd in NSCLC and confirmed the 6 mg/kg dose as optimal for further development. The analysis dataset included 210 patients with NSCLC, with the majority receiving 4 ($n = 50$), 6 ($n = 50$), or 8 mg/kg ($n = 80$) Dato-DXd (Table S5). The PopPK model (structure in Figure S1) described Dato-DXd and DXd concentration-time data well. Covariate effects on Dato-DXd and DXd exposure metrics were generally small (up to ~20% change from the reference), except the weight at 5th and 95th percentiles in the dataset was associated with up to ~30% change in Dato-DXd AUC_{tau} from the reference in the univariate simulations (Figure S2). The parameter estimates of the final models are listed in Tables S6 and S7.

Observed ORRs were similar at the 4, 6, and 8 mg/kg doses (22%, 26%, and 24%, respectively; Table S8). Univariate log-linear logistic regression suggested a positive E–R relationship (Figure S3). Covariate evaluation identified the last prior line of therapy being IO and histology to be significant covariates and identified number of prior lines of therapy, ECOG-PS, and sex to have potentially important effects despite nonsignificance. Once the covariate effects were incorporated into the final multivariate model, the E–R relationship for ORR became steeper (Figure 1; slope estimate: 0.79/ln [μg/mL], 95% CI: 0.14–1.44).

The observed PFS was comparable at the 4, 6, and 8 mg/kg doses based on Kaplan–Meier estimates (Figure S4), with the median PFS time at 6 mg/kg being numerically longer than at the other doses. The univariate Cox modeling identified a significant drug effect on PFS: slope estimate −0.59/ln (μg×day/mL); 95% CI: −0.77 to −0.41. Covariate evaluation found the last prior line of therapy being IO, histology, and sex to be significant and ECOG-PS to have a potentially important effect despite not being statistically significant. The slope (−0.64/ln [μg×day/mL]; 95% CI: −0.83 to −0.45) of drug effect became steeper in the final multivariate Cox model.

The benefit–risk assessment for Dato-DXd was focused on the 4 and 6 mg/kg q3w regimens. Model-simulated results of exposure (steady-state AUC_{tau} of Dato-DXd and DXd), efficacy (ORR and PFS), and safety for these regimens are summarized in Figure 2. The 6 mg/kg dose was expected to have better efficacy than the 4 mg/kg dose due to (1) the simulated mean ORR

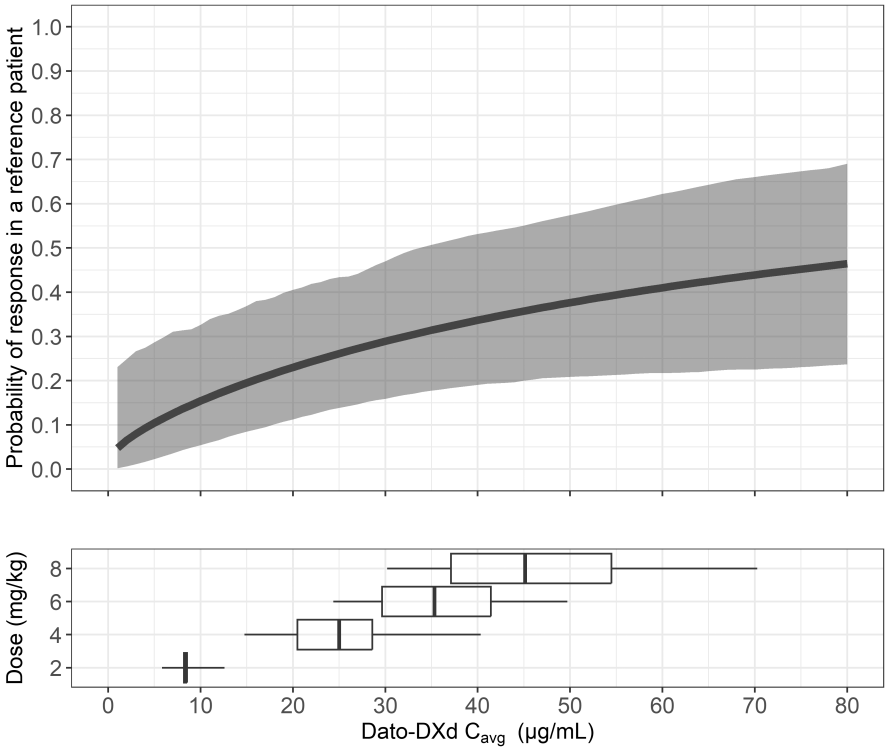

FIGURE 1 Model-derived relationship between exposure (Dato-DXd C_{avg}) and ORR in a reference patient (top) and observed Dato-DXd C_{avg} at different doses (bottom). Top panel: Solid curve and shaded area represent the mean and 95% CI of the C_{avg}-ORR relationship. Bottom panel: Horizontal box plots represent the C_{avg} distributions at the specified dose levels, the whiskers indicate 5th and 95th percentiles, the boxes cover 25th to 75th percentiles, and the vertical bars indicate the medians. C_{avg}, average concentration of Dato-DXd to tumor response or, for those who did not respond, the end of the last dosing cycle up to the data cutoffs; CI, confidence interval; Dato-DXd, datopotamab deruxtecan; ORR, objective response rate.

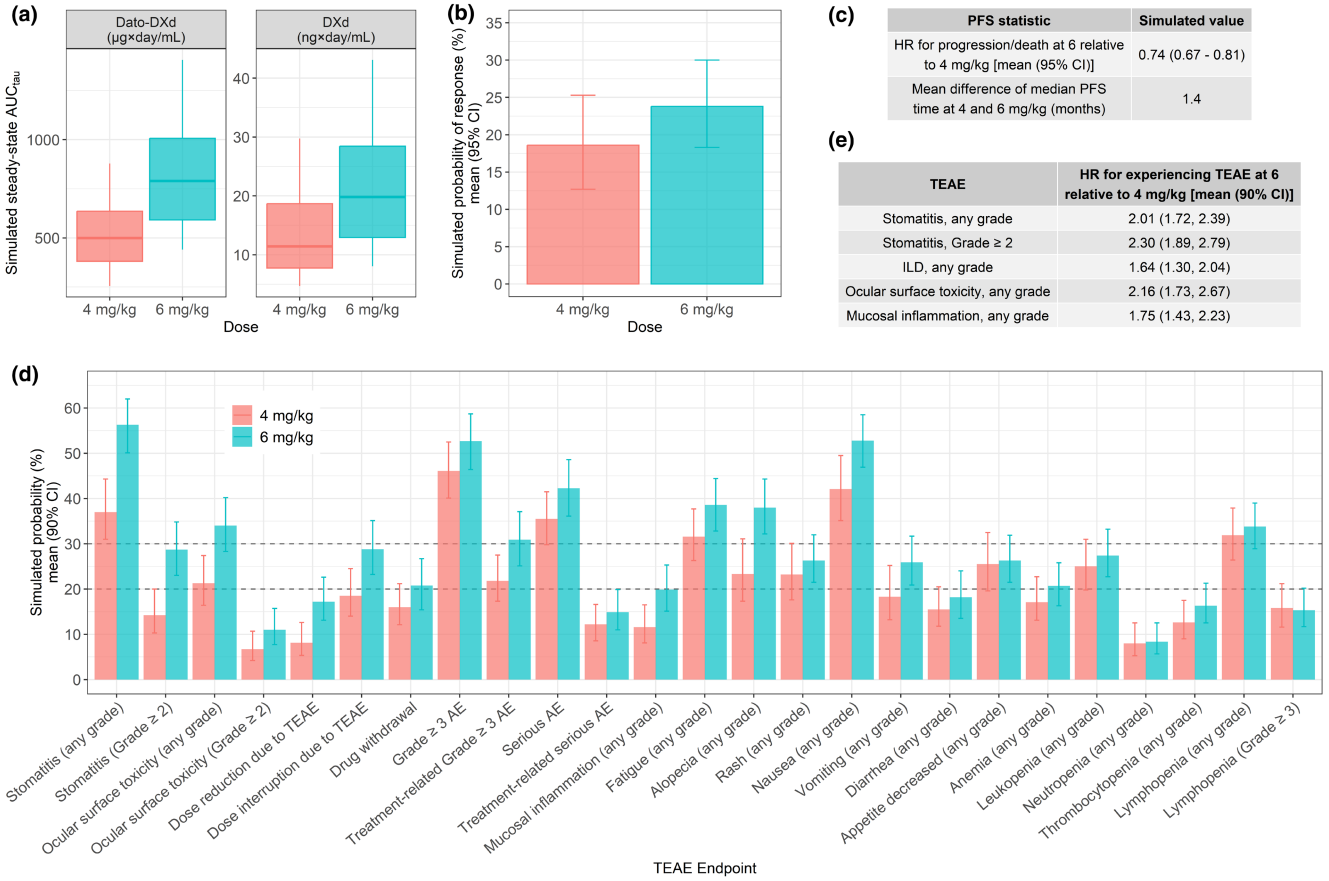

FIGURE 2 Model-simulated results that informed benefit–risk assessment to select 6 mg/kg as an optimal dose for further development. (a) Simulated steady-state AUC_{tau} for Dato-DXd and unconjugated DXd; (b) simulated probability of response (complete or partial response); (c) simulated PFS descriptors; (d) simulated probabilities for indicated TEAEs; and (e) simulated hazard ratios for experiencing the indicated TEAEs when treated with Dato-DXd 6 mg/kg relative to 4 mg/kg in a virtual population with non-small cell lung cancer. Dashed lines represent 20% and 30% probabilities. AE, adverse event; AUC_{tau}, area under the curve over a dosing cycle; CI, confidence interval; Dato-DXd, datopotamab deruxtecan; HR, hazard ratio; ILD, interstitial lung disease; PFS, progression-free survival; TEAE, treatment-emergent adverse event.

being 23.8% (95% CI: 18.3–30.0%) at 6 mg/kg versus 18.6% (95% CI: 12.7–25.3%) at 4 mg/kg; (2) the median PFS time at 6 mg/kg being 1.4 months longer than that at 4 mg/kg; and (3) the HR for progression/death at 6 mg/kg relative to 4 mg/kg being 0.74 (95% CI: 0.67–0.81). The projected safety profile at the 6 mg/kg dose appeared to be less favorable than that at 4 mg/kg. The probabilities for stomatitis (any grade, grade ≥ 2), dose interruption due to TEAEs, ocular surface toxicity, alopecia, and nausea (any grade) from logistic model simulations were expected to be 10.3% to 19.3% higher in the 6 mg/kg than in the 4 mg/kg dose group. The HRs for experiencing stomatitis (any grade, grade ≥ 2), ILD, ocular surface toxicity, and mucosal inflammation (any grade) at the 6 mg/kg dose relative to the 4 mg/kg dose were estimated to be 1.64–2.30. Clinically, the superior efficacy at 6 mg/kg would be expected to offset safety differences relative to the 4 mg/kg dose. Therefore, the 6 mg/kg q3w dose was endorsed for further development of Dato-DXd.

CONCLUSION

We performed an integrated model-based analysis utilizing clinical efficacy, safety, and PK data from the Dato-DXd first-in-human study TROPION-PanTumor01. The first DCO established a positive E–R relationship between all Dato-DXd doses studied, whereas the benefit–risk profile of the second DCO established 6 mg/kg as the optimal dose based on the totality of the evidence. The E–R analysis of the final DCO then confirmed 6 mg/kg to be the optimal dose for late-stage development.

In summary, Dato-DXd 6 mg/kg q3w demonstrated an optimal benefit–risk profile, with superior tumor response and PFS outcomes relative to 4 mg/kg while maintaining manageable safety. Therefore, this dose was recommended for late-phase development. This study showcases the application of model-informed drug development approaches to dose optimization in early oncology development.

AUTHOR CONTRIBUTIONS

Y.L., N.T., S.L., D.S., P.V., D.R.W., and H.Z.-G. wrote the manuscript. Y.L., N.T., S.L., Y.H., K.P., D.R.W., and D.S. designed the research. Y.L., Y.H., K.P., D.R.W., A.P., and D.S. performed the research. Y.L., J.G., Y.H., H.L., K.P., D.R.W., A.P., and P.V. analyzed the data.

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CONFLICT OF INTEREST STATEMENT

H.Z.-G., Y.L., Y.H., A.P., D.S., and N.T. are paid employees of Daiichi Sankyo and own stock in Daiichi Sankyo. J.G., D.S., and P.V. own stock in Daiichi Sankyo. H.L. and D.W. are employees of QuanTx Consulting who provided services to Daiichi Sankyo for this study. S.L. has received support from Daiichi Sankyo and owns stock in Daiichi Sankyo. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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